

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference ET0001PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/EP 03/13469	International filing date (day/month/year) 29/11/2003	(Earliest) Priority Date (day/month/year) 29/11/2002
Applicant LABORATORIOS DEL DR. ESTEVE S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. **Certain claims were found unsearchable** (See Box I).

3. **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

the text is approved as submitted by the applicant.

the text has been established by this Authority to read as follows:

**USE OF 2,5-DIHYDROXYBENZENESULFONIC COMPOUNDS FOR THE TREATMENT OF DISORDERS
BASED ON AN IMPAIRMENT OF NO PRODUCTION AND/OR OF REGULATION OF EDHF FUNCTION**

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

as suggested by the applicant.

because the applicant failed to suggest a figure.

because this figure better characterizes the invention.

None of the figures.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1-7 and 14-25 relate to the treatment of diseases which actually are not well defined. The use of the definitions "for the regulation of nitric oxide (NO) synthesis and/or the regulation of EDHF (Endothelium-Derived-Hyperpolarizing-Factor) in the endothelium of diabetic patients" and "for the prophylaxis and/or treatment of disorders based on an impairment of nitric oxide production and/or impairment of regulation of EDHF function" in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is not fully possible to determine the diseases for which protection might legitimately be sought. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the real and defined diseases mentioned in claims 8-13.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No

1/EP 03/13469

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/185	A61K9/28	A61P3/10	A61P7/00	A61P9/00
	A61P13/12	A61P15/10	A61P27/02		

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EPO-Internal, WPI Data, PAJ, EMBASE, MEDLINE, SCISEARCH, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>RUIZ E ET AL: "Effects of calcium dobesilate on the synthesis of endothelium-dependent relaxing factors in rabbit isolated aorta" BRITISH JOURNAL OF PHARMACOLOGY, vol. 121, no. 4, 1997, pages 711-716, XP001189345 ISSN: 0007-1188 cited in the application abstract page 715, column 1, paragraph 1 - paragraph 2 page 715, column 2, paragraphs 1-4 --- -/-</p>	1-3, 6-9, 12-14

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

19 April 2004

Date of mailing of the international search report

29/04/2004

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/37647 A (ESTEVE SOLER JOSE ;ESTEVE LABOR DR (ES)) 16 October 1997 (1997-10-16) cited in the application the whole document ---	2 ✓ 1-8,10, 12-15,25
Y		16-24
X	REUTER H: "Calcium dobesilate" ZEITSCHRIFT FUR ALLGEMEINMEDIZIN 1975, vol. 51, no. 6, 1975, pages 292-293, XP008029802 the whole document ---	3 ✓ 1-3,6-9, 13-15
X	ADANK C ET AL: "Calcium dobesilate in diabetic retinopathy. A retrospective controlled study." OPHTHALMOLOGICA. JOURNAL INTERNATIONAL D'OPHTALMOLOGIE. INTERNATIONAL JOURNAL OF OPHTHALMOLOGY. ZEITSCHRIFT FUR AUGENHEILKUNDE, (1985) 190 (2) 102-11. , XP008029583 abstract table I page 105, column 1, paragraph 3 page 108, column 2, paragraph 2 - paragraph 3 page 110, column 1, paragraph 1 ---	4 ✓ 1-3,6-9, 14,15
X	KEDZIORA-KORNATOWSKA K ET AL: "The effect of calcium dobesilate on lipid peroxidation and antioxidative defense in diabetic kidney" NEPHROLOGY DIALYSIS TRANSPLANTATION, vol. 16, no. 6, June 2001 (2001-06), page A78 XP008029588 Annual Congress of the European Renal Association and the European Dialysis and Transplant Association; Vienna, Austria; June 24-27, 2001 ISSN: 0931-0509 the whole document ---	5 ✓ 1-3,6,7, 11,14
X	TEJERINA T ET AL: "Calcium dobesilate: Pharmacology and future approaches" GENERAL PHARMACOLOGY, vol. 31, no. 3, September 1998 (1998-09), pages 357-360, XP002233076 ISSN: 0306-3623 abstract page 357, column 1, paragraph 3 page 357, column 2, paragraph 1 - paragraph 2 ---	6 ✓ 1-3,6-9, 12-15
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GUERRINI M ET AL: "Calcium dobesilate in the treatment of diabetic microangiopathy: a chronic controlled open study on the hemorheological and microcirculatory changes" RIFORMA MEDICA 1988 ITALY, vol. 103, no. 1-2, 1988, pages 7-12, XP008029582 ISSN: 0035-5259 abstract page 8, column 1, paragraph 4 page 11, column 2, paragraph 2 ---</p>	7 1-3,6-9, 11,13-15
X	<p>DATABASE EMBASE 'Online' ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; 1973 TEMPRANO ACEDO J: "Clinical trials of calcium dobesilate in diabetic retinopathy" Database accession no. EMB-1974137352 XP002276559 abstract & ANALES DEL INSTITUTO BARRAQUER 1973, vol. 11, no. 1-2, 1973, pages 9-16, ---</p>	8 1-9,14, 15
Y	<p>FR 2 656 525 A (DELALANDE SA) 5 July 1991 (1991-07-05) page 2, line 23 - line 32 page 4, line 21 - line 25 example 3 claim 1 ---</p>	9 16-19,22
Y	<p>DE 100 16 356 A (BEISEL GUENTHER) 4 October 2001 (2001-10-04) column 1, paragraph 1 - paragraph 2 column 2, paragraph 12 column 3, paragraphs 17,19,20 column 4, paragraphs 26,27 column 7, paragraph 63 column 8, paragraph 87 column 9, paragraphs 95,96 claims 1-4,8 ---</p>	17-24 w ✓
		-/-

INTERNATIONAL SEARCH REPORT

National Application No

1/EP 03/13469

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>ANGULO JAVIER ET AL: "Calcium dobesilate potentiates endothelium-derived hyperpolarizing factor-mediated relaxation of human penile resistance arteries." BRITISH JOURNAL OF PHARMACOLOGY, vol. 139, no. 4, June 2003 (2003-06), pages 854-862, XP001189343 ISSN: 0007-1188 (ISSN print) abstract page 855, column 2, paragraph 2 page 860, column 1, paragraph 3 page 860, column 2, paragraph 2 - paragraph 3</p> <p>---</p>	11 1-3,6-8, 10,14
T	<p>ANGULO JAVIER ET AL: "Diabetes impairs endothelium-dependent relaxation of human penile vascular tissues mediated by NO and EDHF." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 312, no. 4, 26 December 2003 (2003-12-26), pages 1202-1208, XP004476405 ISSN: 0006-291X abstract page 1203, column 1, paragraph 2 figure 6 page 1205, column 1, paragraph 1 -page 1206, column 1, paragraph 2 page 1206, column 2, paragraph 3</p> <p>-----</p>	12 1-3,6,7, 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/13469

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/13469

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9737647	A	16-10-1997	FR	2747040 A1	10-10-1997
			WO	9737647 A1	16-10-1997
			AU	715600 B2	03-02-2000
			AU	2693697 A	29-10-1997
			BR	9708595 A	03-08-1999
			EP	0954298 A1	10-11-1999
			JP	2000508308 T	04-07-2000
			NO	984572 A	30-09-1998
			US	6147112 A	14-11-2000
			US	6403643 B1	11-06-2002
			CA	2251226 A1	16-10-1997
			ES	2127132 A1	01-04-1999
FR 2656525	A	05-07-1991	FR	2656525 A1	05-07-1991
DE 10016356	A	04-10-2001	DE	10016356 A1	04-10-2001
			DE	20023135 U1	03-04-2003